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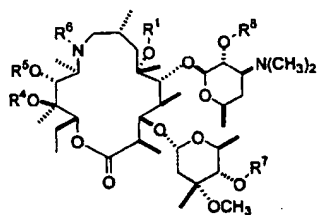
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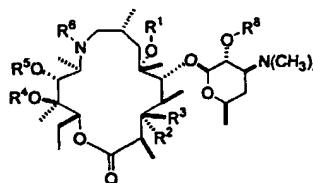
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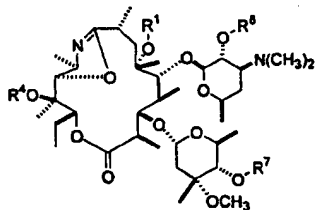
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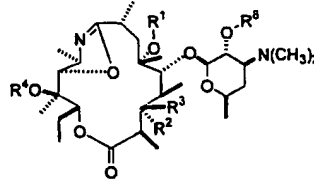
(I)



(II)



(III)



(IV)

(57) Abstract: Compounds of formula (I), formula (II), formula (III), and formula (IV) or pharmaceutically acceptable salts or prodrugs thereof, are antibacterial agents. Compositions containing the compounds, processes for making the compounds, synthetic intermediates employed in the processes, and methods for treatment and prevention of bacterial infections are disclosed.

WO 01/14397 A1

9A-AZALIDES WITH ANTIBACTERIAL ACTIVITY

Technical Field

The instant invention relates to 9a-azalides which are antibacterial agents, compositions containing the compounds, processes for making the compounds, synthetic intermediates employed in the processes, and methods for treatment and prevention of bacterial infections.

Background of The Invention

Macrolide antibacterial agents are widely used to treat and prevent bacterial infections. However, the discovery of bacterial strains which have resistance or insufficient susceptibility to macrolide antibacterial agents has promoted development of compounds with modified or improved profiles of antibiotic activity. One such class of compounds are azalides such as azithromycin, referred to in United States patents 4,474,768 and 4,517,359. Azalides are macrolide antibacterial agents with a core ring structurally similar to the erythronolide A or B ring except for the presence of a substituted or unsubstituted nitrogen moiety at the 9a position. Because of the potential for azalides to display modified or improved profiles of antibiotic activity, they are the subject of current research for their clinical potential.

PCT Application WO 98/56801, published December 17, 1998 discloses a series of 9a-(N-(alkyl))-azalide erythromycin A derivatives and a series of 9a-(N-(alkyl))-azalide 6-O-methylerythromycin A derivatives.

PCT Application WO 98/56802, published December 17, 1998 discloses a series of 9a-(N(H))-azalide erythromycin A derivatives and a series of 9a-(N(H))-azalide 6-O-methylerythromycin A derivatives.

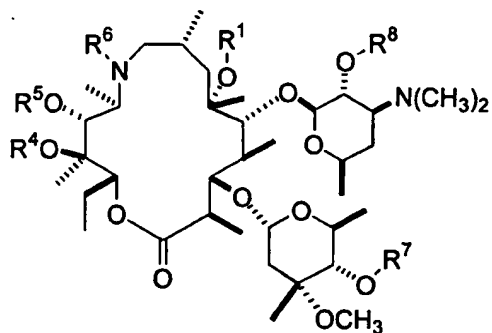
PCT Application WO 99/00124, published January 7, 1999, discloses a series of 9a-(N(R_n))- azalide 3-thiooxyerythromycin A derivatives and a series of 9a-(N(R_n))-azalide 6-O-methyl-3-oxoerythromycin A derivatives, wherein R_n is an optionally substituted alkyl or heteroalkyl.

PCT Application WO 99/00125, published January 7, 1999, discloses a series of 9a-(N(R_n))- azalide 3-oxoerythromycin A derivatives and a series of 9a-(N(R_n))-azalide 6-O-methyl-3-oxoerythromycin A derivatives, wherein R_n is an optionally substituted alkyl or heteroalkyl.

United States patent 5,686,587 discloses a synthesis of azithromycin comprising introducing a 9a-(N(H))- moiety to erythromycin A by oxime formation, Beckman rearrangement, reduction, and methylation.

Summary of The Invention

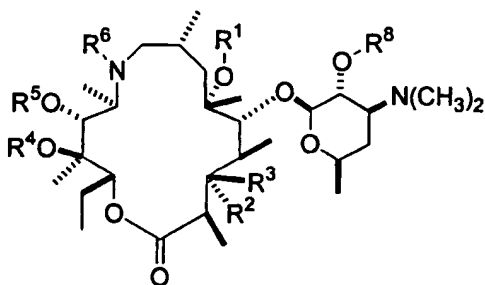
In one embodiment of the present invention are disclosed compounds of formula (I)



(I),

5

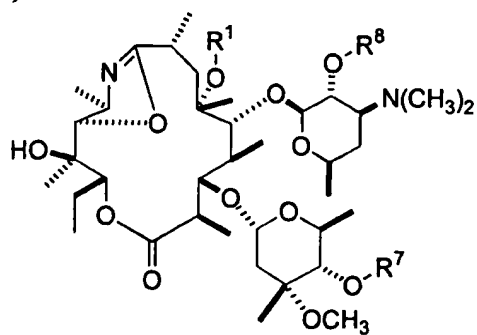
compounds of formula (II)



(II),

10

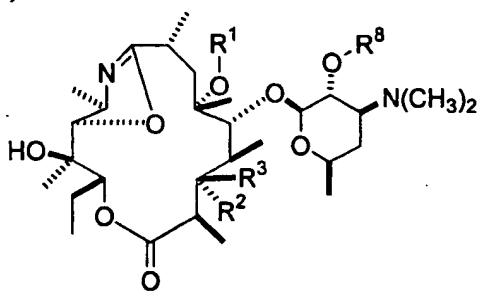
compounds of formula (III)



(III),

and

compounds of formula (IV)



(IV),

or pharmaceutically acceptable salts or prodrugs thereof, wherein, in formulas (I)-(IV),

5 R¹ and R⁶ are independently selected from the group consisting of

- (1) hydrogen,
- (2) -C₁-C₁₂-alkyl,
- (3) -C₃-C₁₂-alkenyl,

and

10 (4) -C₃-C₁₂-alkynyl,

wherein (2)-(4) can be optionally substituted with one, two, or three substituents independently selected from the group consisting of

(a) halogen,

(b) -OR⁹, wherein R⁹ is selected from the group consisting of

- 15 (i) hydrogen,
- (ii) -C₁-C₁₂-alkyl,
- (iii) -C₂-C₁₂-heteroalkyl,

wherein (ii) and (iii) can be optionally substituted with one, two, or three substituents independently selected from the group consisting of

- 20 (1') aryl,
 - (2') substituted aryl,
 - (3') heteroaryl,
- and
- (4') substituted heteroaryl,

- 25 (iv) aryl,
 - (v) substituted aryl,
 - (vi) heteroaryl,
- and
- (vii) substituted heteroaryl,

30 (c) -NR¹¹R¹², wherein R¹¹ and R¹² are independently selected from the group consisting of

- (i) hydrogen,

- (ii) -C₁-C₁₂-alkyl,
- (iii) -C₂-C₁₂-heteroalkyl,

wherein (ii) and (iii) can be optionally substituted with one, two, or three substituents independently selected from the group consisting of

- (1') aryl,
- (2') substituted aryl,
- (3') heteroaryl,
- and
- (4') substituted heteroaryl,

- (iv) aryl,
- (v) substituted aryl,
- (vi) heteroaryl,
- and
- (vii) substituted heteroaryl,

or

R¹¹ and R¹², together with the atom to which they are attached, form a heterocycloalkyl ring, wherein the heterocycloalkyl ring can be optionally substituted,

(d) =N-O-R⁹, wherein R⁹ is defined above,

- (e) aryl,
- (f) substituted aryl,
- (g) heteroaryl,
- (h) substituted heteroaryl,

- (i) -C₃-C₈-cycloalkyl,
- (j) substituted -C₃-C₈-cycloalkyl,
- (k) heterocycloalkyl,
- (l) substituted heterocycloalkyl,

(m) -NHC(O)R⁹, wherein R⁹ is defined above,

(n) -NHC(O)OR¹⁰, wherein R¹⁰ is selected from the group consisting of

- (i) -C₁-C₁₂-alkyl,
- (ii) -C₁-C₁₂-heteroalkyl,

wherein (i) and (ii) can be optionally substituted with one, two, or three substituents independently selected from the group consisting of

- (1') aryl,
- (2') substituted aryl,
- (3') heteroaryl,
- and

(4') substituted heteroaryl,

(iii) aryl,

(iv) substituted aryl,

(v) heteroaryl,

5 and

(vi) substituted heteroaryl,

(o) -NHC(O)NR¹¹R¹², wherein R¹¹ and R¹² are defined above,

(p) -OC(O)R¹⁰, wherein R¹⁰ is defined above,

(q) -OC(O)OR¹⁰, wherein R¹⁰ is defined above,

10 (r) -OC(O)NR¹¹R¹², wherein R¹¹ and R¹² are defined above,

(s) -C(O)R⁹, wherein R⁹ is defined above,

(t) -CO₂R⁹, wherein R⁹ is defined above,

and

(u) -C(O)NR¹¹R¹², wherein R¹¹ and R¹² are defined above;

15

R² is hydrogen;

R³ is -OR¹³, wherein R¹³ is selected from the group consisting of

(1) hydrogen,

20 (2) -C(O)R¹⁰, wherein R¹⁰ is defined above,

(3) -CO₂R¹⁰, wherein R¹⁰ is defined above,

and

(4) -C(O)NR¹¹R¹², wherein R¹¹ and R¹² are defined above;

25 or

R² and R³ together are oxo;

R⁴ and R⁵ are hydrogen;

30 or

R⁴ and R⁵ together are -C(O)- or -(CH₂)_x-, wherein x is one, two, or three;

or

R⁵ and R⁶ together are -C(O)- or -(CH₂)_x-, wherein x is defined above;

35

R⁷ is selected from the group consisting of

(1) hydrogen,

- (2) -C₁-C₁₂-alkyl,
(3) -C₃-C₁₂-alkenyl,
(4) -C₃-C₁₂-alkynyl,
(5) -C₂-C₁₂-heteroalkyl,
5 (6) -C₄-C₁₂-heteroalkenyl,
(7) -C₄-C₁₂-heteroalkynyl,

wherein (2)-(7) can be optionally substituted with one, two, or three substituents independently selected from the group consisting of

- (a) halo,
10 (b) hydroxy,
(c) -NR¹¹R¹², wherein R¹¹ and R¹² are defined above,
(d) aryl,
(e) substituted aryl,
(f) heteroaryl,

15 and

- (g) substituted heteroaryl,
(8) -C(O)R⁹, wherein R⁹ is defined above,
(9) -CO₂R⁹, wherein R⁹ is defined above,
and
20 (11) -C(O)NR¹¹R¹², wherein R¹¹ and R¹² are defined above;

and

R⁸ is hydrogen or a hydroxy protecting group;

25 with the proviso that when R² and R³ together are oxo, R¹ is other than hydrogen or unsubstituted methyl.

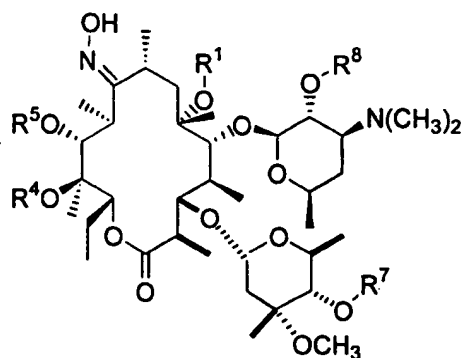
In another embodiment of the present invention are disclosed pharmaceutical compositions comprising a pharmaceutically effective amount of the compounds in combination with a pharmaceutically acceptable carrier.

30 In still another embodiment of the present invention are disclosed methods of treating a bacterial infection in a mammal in need of such treatment which comprises administering to the mammal a therapeutically effective amount of the compounds.

In still yet another embodiment of the present invention is disclosed a method for preparing the compounds,

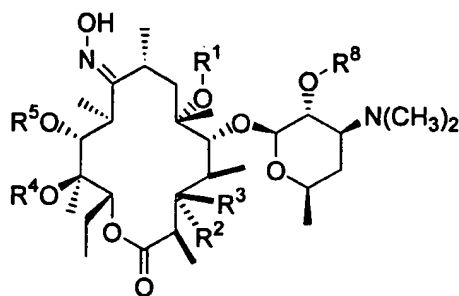
35 the method comprising

- (a) reacting compounds of formula (Ia)



(Ia)

or compounds of formula (Ib)



(Ib),

wherein R¹, R², R³, R⁴, R⁵, R⁷, and R⁸ are defined above,
with an oxime activating agent;

(b) optionally reacting the product from step (a) with a reducing agent;

10 (c) optionally alkylating the product from step (b);

and

(d) optionally deprotecting the product from step (c).

Detailed Description of The Invention

15 The term "alkenyl," as used herein, refers to a monovalent straight or branched chain group containing at least one carbon-carbon double bond. The alkenyl groups of this invention can be optionally substituted.

The term "alkyl," as used herein, refers to saturated, straight or branched chain hydrocarbon radicals. Examples of alkyl radicals include methyl, ethyl, propyl, iso-
20 propyl, n-butyl, *tert*-butyl, neo-pentyl, and n-hexyl. The alkyl groups of this invention can be optionally substituted.

The term "-C₁-C₃-alkylamino," as used herein, refers to a amino group, as defined herein wherein one hydrogen atom is replaced by a -C₁-C₃-alkyl group. Examples of -C₁-C₃-alkylamino include methylamine, ethylamine, propylamine, and iso-
25 propylamine.

The term "-C₁-C₃-alkylthio," as used herein, refers to a -C₁-C₃-alkyl group, as defined herein, attached to the parent molecular group through a sulfur atom. Examples of -C₁-C₃-alkylthio include methyl sulfide, ethyl sulfide, propyl sulfide, and iso-propyl sulfide.

5 The term "alkoxy," as used herein, refers to an alkyl group, as previously defined, attached to the parent molecular group through an oxygen atom. Examples of alkoxy include methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, *tert*-butoxy, neo-pentoxy and n-hexoxy. The alkoxy groups of this invention can be optionally substituted.

10 The term "alkynyl," as used herein, refers to a monovalent straight or branched chain group of two to six carbon atoms containing at least one carbon-carbon triple bond. Examples of alkynyl include ethynyl, propynyl, and butynyl. The alkynyl groups of this invention can be optionally substituted.

The term "amino," as used herein, refers to -NH₂.

15 The term "aprotic solvent," as used herein, refers to a solvent that is relatively inert to proton activity, i.e., not acting as a proton donor. Examples include hydrocarbons such as hexane and toluene, halogenated hydrocarbons such as dichloromethane, ethylene chloride, and chloroform, heterocyclic compounds such as tetrahydrofuran and N-methylpyrrolidinone, and ethers such as diethyl ether, bis-methoxymethyl ether. Such compounds are well known to those skilled in the art, and it will be obvious to those
20 skilled in the art that individual solvents or mixtures thereof can be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of aprotic solvents can be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick, et al., Vol. II, in the Techniques of
25 Chemistry Series, John Wiley & Sons, NY, 1986, the relevant portions of which are incorporated herein by reference.

The term "aryl" as used herein refers to unsubstituted carbocyclic aromatic groups including phenyl, naphthyl, and anthracenyl.

30 The term "arylamino," as used herein, refers to a amino group, as defined herein wherein one hydrogen atom is replaced by an aryl group, as defined herein.

The term "aryloxy," as used herein, refers to an aryl group, as defined herein, attached to the parent molecular group through an oxygen atom.

35 The term "arylthio," as used herein, refers to an aryl group, as defined herein, attached to the parent molecular group through a sulfur atom.

The term "azido," as used herein, refers to -N₃.

The term "benzyl," as used herein, refers to -CH₂C₆H₅.

The term "benzyloxy," as used herein, refers to a benzyl group, as defined herein, attached to the parent molecular group through an oxygen atom.

The term "benzylamino," as used herein, refers to a amino group, as defined herein wherein one hydrogen atom is replaced by a benzyl group, as defined herein.

5 The term "benzylthio," as used herein, refers to an benzyl group, as defined herein, attached to the parent molecular group through a sulfur atom.

The term "carboxaldehyde," as used herein, refers to -CHO.

The term "cyano," as used herein, refers to -CN.

10 The term "cycloalkyl," as used herein, refers to saturated carbocyclic groups having three to seven carbons such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

The term "halo," as used herein, refers to -F, -Cl, -Br, and -I.

15 The term "heteroalkenyl," as used herein, refers to an alkenyl group having from four to twelve atoms, wherein at least atom is replaced with a group selected from -O-, =N-, -N(H)-, -N(CH₃)-, -C(O)-, -S(O)_n-, or a combination thereof, and the remaining atoms are carbon. The heteroalkenyl groups of this invention can be optionally substituted.

20 The term "heteroalkyl," as used herein, refers to an alkyl group having from two to twelve atoms, wherein at least atom is replaced with a group selected from -O-, =N-, -N(H)-, -N(CH₃)-, -C(O)-, -S(O)_n-, or a combination thereof, and the remaining atoms are carbon. The heteroalkyl groups of this invention can be optionally substituted.

25 The term "heteroalkynyl," as used herein, refers to an alkynyl group having from four to twelve atoms, wherein at least atom is replaced with a group selected from -O-, =N-, -N(H)-, -N(CH₃)-, -C(O)-, -S(O)_n-, or a combination thereof, and the remaining atoms are carbon. The heteroalkynyl groups of this invention can be optionally substituted.

30 The term "heteroaryl," as used herein, refers to a cyclic aromatic group having five or six ring atoms wherein at least one ring atom is selected from the group consisting of oxygen, sulfur, and nitrogen, and the remaining ring atoms are carbon. The nitrogen atoms can optionally be quaternized, and the sulfur atoms can optionally be oxidized. Heteroaryl groups of this invention include those derived from furan, imidazole, isothiazole, isoxazole, oxadiazole, oxazole, 1,2,3-oxadiazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrroline, quinoline, thiazole, 1,3,4-thiadiazole, thiene, triazole, and tetrazole.

35 The term "heteroarylamino," as used herein, refers to a amino group, as defined herein wherein one hydrogen atom is replaced by a heteroaryl group, as defined herein.

The term "heteroaryloxy," as used herein, refers to a heteroaryl group, as defined herein, attached to the parent molecular group through an oxygen atom.

The term "heteroarylthio," as used herein, refers to a heteroaryl group, as defined herein, attached to the parent molecular group through a sulfur atom.

5 The term "heterocycloalkyl" as used herein, refers to a non-aromatic five-, six- or seven-membered ring or a bi- or tri-cyclic group comprising fused six-membered rings having between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen wherein each 5-membered ring has zero to one double bonds and each six-membered ring has zero to 2 double bonds. The nitrogen and sulfur heteroatoms can
10 optionally be oxidized, the nitrogen heteroatom can optionally be quaternized, and any of the above heterocyclic rings can be fused to a benzene ring. Representative heterocycles include, but are not limited to, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazoliny, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl. The heterocycloalkyl groups of this
15 invention can be optionally substituted with one, two, three, or four substituents independently selected from -F, -Cl, -Br, -I, -OH, -NO₂, -CN, -C(O)-C₁-C₆-alkyl, -C(O)-aryl, -C(O)-heteroaryl, -CO₂-alkyl, -CO₂-aryl, -CO₂-heteroaryl, -CONH₂, -CONH-C₁-C₆-alkyl, -CONH-aryl, -CONH-heteroaryl, -OC(O)-C₁-C₆-alkyl, -OC(O)-aryl, -OC(O)-heteroaryl, -OCO₂-alkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCONH₂, -OCONH-C₁-C₆-alkyl, -OCONH-aryl, -OCONH-heteroaryl, -NHC(O)-C₁-C₆-alkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHCO₂-alkyl, -NHCO₂-aryl, -NHCO₂-heteroaryl, -NHCONH₂, -NHCONH-C₁-C₆-alkyl, -NHCONH-aryl, -NHCONH-heteroaryl, -SO₂-C₁-C₆-alkyl, -SO₂-aryl, -SO₂-heteroaryl, -SO₂NH₂, -SO₂NH-C₁-C₆-alkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -C₁-C₆-alkyl, -C₃-C₆-cycloalkyl, -CF₃, -CH₂CF₃, -CHCl₂, -CH₂OH, -
20 CH₂CH₂OH, -CH₂NH₂, -CH₂SO₂CH₃, aryl, heteroaryl, benzyl, benzyloxy, aryloxy, heteroaryloxy, -C₁-C₆-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, -C₁-C₃-alkylamino, thio, arylthio, heteroarylthio, benzylthio, -C₁-C₆-alkylthio, or methylthiomethyl.

The term "hydroxy," as used herein, refers to -OH.

30 The term "hydroxy protecting group", as used herein, refers to an easily removable group to which are known in the art to protect a hydroxyl group against undesirable reaction during synthetic procedures and to be selectively removable. The use of hydroxy-protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, cf, for
35 example, T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991), the relevant portions of which are incorporated herein by reference. Examples of hydroxy-protecting groups include,

methylthiomethyl, *tert*-dimethylsilyl, *tert*-butyldiphenylsilyl, acyl substituted with an aromatic group, and the like.

The term "methoxymethoxy," as used herein, refers to -OCH₂OCH₃.

The term "methoxyethoxy," as used herein, refers to -OCH₂OCH₂CH₃.

5 The term "methylthiomethyl," as used herein, refers to -CH₂SCH₃.

The term "oxo," as used herein, refers to a group formed by the replacement of two hydrogen atoms on the same carbon atom of an alkyl group, as defined above, with a single oxygen atom and is exemplified by a carbonyl group.

10 A the term "protected hydroxy" refers to a hydroxy group protected with a hydroxy protecting group, as defined above, such as benzoyl, acetyl, trimethylsilyl, triethylsilyl, or methoxymethyl groups.

The term "substituted aryl," as used herein, refers to an aryl group, as defined herein, substituted by independent replacement of one, two or three of the hydrogen atoms thereon with -F, -Cl, -Br, -I, -OH, -NO₂, -CN, -C(O)-C₁-C₆-alkyl, -C(O)-
 15 heteroaryl, -CO₂-alkyl, -CO₂-aryl, -CO₂-heteroaryl, -CONH₂, -CONH-C₁-C₆-alkyl, -CONH-aryl, -CONH-heteroaryl, -OC(O)-C₁-C₆-alkyl, -OC(O)-aryl, -OC(O)-heteroaryl, -OCO₂-alkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCONH₂, -OCONH-C₁-C₆-alkyl, -OCONH-aryl, -OCONH-heteroaryl, -NHC(O)-C₁-C₆-alkyl, -NHC(O)-aryl, -NHC(O)-
 20 heteroaryl, -NHCO₂-alkyl, -NHCO₂-aryl, -NHCO₂-heteroaryl, -NHCONH₂, -NHCONH-C₁-C₆-alkyl, -NHCONH-aryl, -NHCONH-heteroaryl, -SO₂-C₁-C₆-alkyl, -SO₂-aryl, -SO₂-heteroaryl, -SO₂NH₂, -SO₂NH-C₁-C₆-alkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -C₁-C₆-alkyl, -C₃-C₆-cycloalkyl, -CF₃, -CH₂CF₃, -CHCl₂, -CH₂OH, -CH₂CH₂OH, -CH₂NH₂, -CH₂SO₂CH₃, aryl, heteroaryl, benzyl, benzyloxy, aryloxy, heteroaryloxy, -C₁-C₆-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino,
 25 -C₁-C₃-alkylamino, thio, arylthio, heteroarylthio, benzylthio, -C₁-C₆-alkylthio, or methylthiomethyl.

The term "substituted heteroaryl" as used herein refers to a heteroaryl group as defined herein substituted by independent replacement of one, two or three of the hydrogen atoms thereon with -F, -Cl, -Br, -I, -OH, -NO₂, -CN, -C(O)-C₁-C₆-alkyl, -C(O)-
 30 aryl, -C(O)-heteroaryl, -CO₂-alkyl, -CO₂-aryl, -CO₂-heteroaryl, -CONH₂, -CONH-C₁-C₆-alkyl, -CONH-aryl, -CONH-heteroaryl, -OC(O)-C₁-C₆-alkyl, -OC(O)-aryl, -OC(O)-heteroaryl, -OCO₂-alkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCONH₂, -OCONH-C₁-C₆-alkyl,
 35 -OCONH-aryl, -OCONH-heteroaryl, -NHC(O)-C₁-C₆-alkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHCO₂-alkyl, -NHCO₂-aryl, -NHCO₂-heteroaryl, -NHCONH₂, -NHCONH-C₁-C₆-alkyl, -NHCONH-aryl, -NHCONH-heteroaryl, -SO₂-C₁-C₆-alkyl, -SO₂-aryl, -SO₂-

heteroaryl, -SO₂NH₂, -SO₂NH-C₁-C₆-alkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -C₁-C₆-alkyl, -C₃-C₆-cycloalkyl, -CF₃, -CH₂CF₃, -CHCl₂, -CH₂OH, -CH₂CH₂OH, -CH₂NH₂, -CH₂SO₂CH₃, aryl, heteroaryl, benzyl, benzyloxy, aryloxy, heteroaryloxy, -C₁-C₆-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, -C₁-C₃-alkylamino, thio, arylthio, heteroarylthio, benzylthio, -C₁-C₆-alkylthio, or methylthiomethyl.

The term "substituted heterocycloalkyl," as used herein, refers to a heterocycloalkyl group, as defined above, substituted by independent replacement of one, two or three of the hydrogen atoms thereon with -F, -Cl, -Br, -I, -OH, -NO₂, -CN, -C(O)-C₁-C₆-alkyl,

-C(O)-aryl, -C(O)-heteroaryl, -CO₂-alkyl, -CO₂-aryl, -CO₂-heteroaryl, -CONH₂, -CONH-C₁-C₆-alkyl, -CONH-aryl, -CONH-heteroaryl, -OC(O)-C₁-C₆-alkyl, -OC(O)-aryl, -OC(O)-heteroaryl, -OCO₂-alkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCONH₂, -OCONH-C₁-C₆-alkyl, -OCONH-aryl, -OCONH-heteroaryl, -NHC(O)-C₁-C₆-alkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHCO₂-alkyl, -NHCO₂-aryl, -NHCO₂-heteroaryl, -NHCONH₂, -NHCONH-C₁-C₆-alkyl, -NHCONH-aryl, -NHCONH-heteroaryl, -SO₂-C₁-C₆-alkyl, -SO₂-aryl, -SO₂-heteroaryl, -SO₂NH₂, -SO₂NH-C₁-C₆-alkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -C₁-C₆-alkyl, -C₃-C₆-cycloalkyl, -CF₃, -CH₂CF₃, -CHCl₂, -CH₂OH, -CH₂CH₂OH,

-CH₂NH₂, -CH₂SO₂CH₃, aryl, heteroaryl, benzyl, benzyloxy, aryloxy, heteroaryloxy, alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, -C₁-C₃-alkylamino, thio, arylthio, heteroarylthio, benzylthio, alkylthio, or methylthiomethyl.

The term "thio," as used herein, refers to -SH.

Numerous asymmetric centers exist in the compounds of the present invention. Except where otherwise noted, the present invention contemplates the various stereoisomers and mixtures thereof. Accordingly, whenever a bond is represented by a wavy line or a straight line, it is intended that a mixture of stereo-orientations or an individual isomer of unassigned orientation can be present.

The term "pharmaceutically acceptable prodrugs," as used herein refers to, those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention.

The term "prodrug," as used herein, represents compounds which are rapidly transformed *in vivo* to parent compounds defined above, for example, by hydrolysis in

blood. A thorough discussion is provided in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, the relevant portions of which are incorporated herein by reference.

5 The term "pharmaceutically acceptable salt," as used herein, refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, and allergic response and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describe
10 pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977), the relevant portions of which are incorporated herein by reference. The salts can be prepared in situ during the final isolation and purification of the compounds of the invention or separately by reacting a free base group with a suitable organic acid. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an
15 amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate,
20 bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laureate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate,
25 pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, and valerate. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, and magnesium. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium,
30 and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate, and aryl sulfonate.

 The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term
35 "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as

lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laureate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms can contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

5 In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, can depend upon crystal size and crystalline form. Alternatively, delayed
10 absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microcapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of
15 other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-
20 irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one
25 inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca
30 starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and
35 mixtures thereof. In the case of capsules, tablets and pills, the dosage form can also comprise buffering agents.

Solid compositions of a similar type can also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

5 The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They can optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances
10 and waxes.

Solid compositions of a similar type can also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

15 The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms can also comprise, as is
20 normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms can also comprise buffering agents. They can optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal
25 tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a
30 pharmaceutically acceptable carrier and any needed preservatives or buffers as can be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels can contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes,
35 paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

5 Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

10 According to the methods of treatment of the present invention, bacterial infections are treated or prevented in a patient such as a human or lower mammal by administering to the patient a therapeutically effective amount of a compound of the invention, in such amounts and for such time as is necessary to achieve the desired result. By a "therapeutically effective amount" of a compound of the invention is meant a sufficient
15 amount of the compound to treat bacterial infections, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of
20 factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound
25 employed; and like factors well known in the medical arts.

The total daily dose of the compounds of this invention administered to a human or other mammal in single or in divided doses can be in amounts, for example, from 0.01 to 50 mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose compositions can contain such amounts or submultiples thereof to make up the daily dose.
30 In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of this invention per day in single or multiple doses.

Preferred compounds of the invention include:

Compound of formula (II): R^2 is hydrogen, R^3 is $-OR^{13}$, and R^{13} is hydrogen.

35 Compound of formula (II): R^2 and R^3 together are oxo.

Compound of formula (I): R^4 and R^5 are hydrogen.

Compound of formula (I): R^4 and R^5 are hydrogen.

Compound of formula (II): R⁴ and R⁵ together are -C(O)-.

Compound of formula (I): R⁶ is hydrogen.

Compound of formula (I): R⁶ is methyl.

Compound of formula (II): R⁶ is methyl.

5 Compound of formula (I): R¹ is -CH₂-CH=CH₂.

Compound of formula (II): R¹ is -CH₂-CH=CH₂.

Compound of formula (I): R¹ is -CH₂-CH=CH-(3-quinolinyl).

and

Compound of formula (II): R¹ is -CH₂-CH=CH-(3-quinolinyl).

10 Specific compounds of the invention include:

Compound of formula (III): R¹ is -CH₂CH=CH₂, R⁴ is hydrogen, R⁷ is hydrogen, R⁸ is hydrogen,

Compound of formula (I): R¹ is -CH₂CH=CH₂, R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is hydrogen, R⁷ is hydrogen, R⁸ is hydrogen,

15 Compound of formula (I): R¹ is -CH₂CH=CH₂, R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is methyl, R⁷ is hydrogen, R⁸ is hydrogen,

Compound of formula (II): R¹ is -CH₂CH=CH-(3-quinolinyl), R² and R³ together are oxo, R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is methyl, R⁸ is hydrogen,

20 Compound of formula (II): R¹ is -CH₂CH=CH-(3-quinolinyl), R² and R³ together are oxo, R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is methyl, R⁸ is hydrogen,

Compound of formula (II): R¹ is -CH₂CH=CH-(3-quinolinyl), R² and R³ together are oxo, R⁴ and R⁵ together are -C(O)-, R⁶ is methyl, R⁸ is -C(O)CH₃,

and

25 Compound of formula (I): R¹ is -CH₂CH=CH-(3-quinolinyl), R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is methyl, R⁷ is hydrogen, R⁸ is hydrogen.

Determination of Biological Activity

In Vitro Assay of Antibacterial Activity

30 Representative compounds of the present invention were assayed *in vitro* for antibacterial activity as follows: Twelve petri dishes containing successive aqueous dilutions of the test compound mixed with 10 mL of sterilized Brain Heart Infusion (BHI) agar (Difco 0418-01-5) were prepared. Each plate was inoculated with 1:100 (or 1:10 for slow-growing strains, such as Micrococcus and Streptococcus) dilutions of up to 32 different microorganisms, using a Steers replicator block. The inoculated plates were
35 incubated at 35-37 °C for 20 to 24 hours. In addition, a control plate, using BHI agar containing no test compound, was prepared and incubated at the beginning and end of each test.

An additional plate containing a compound having known susceptibility patterns for the organisms being tested and belonging to the same antibiotic class as the test compound was also prepared and incubated as a further control, as well as to provide test-to-test comparability. Erythromycin A was used for this purpose.

5 After incubation, each plate was visually inspected. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of drug yielding no growth, a slight haze, or sparsely isolated colonies on the inoculum spot as compared to the growth control. The results of this assay, shown below in Table 1, demonstrate the antibacterial activity of the compounds of the invention.

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Microorganism	Code
Staphylococcus aureus ATCC 6538P	AA

Staphylococcus aureus A-5177	BB
Staphylococcus aureus A-5278	CC
Staphylococcus aureus CMX 642A	DD
Staphylococcus aureus NCTC 10649M	EE
Staphylococcus aureus CMX 553	FF
Staphylococcus aureus 1775	GG
Staphylococcus epidermidis 3519	HH
Enterococcus faecium ATCC X043	II
Streptococcus bovis A-5169	JJ
Streptococcus agalactiae CMX 508	KK
Streptococcus pyogenes EES61	LL
Streptococcus pyogenes 930	MM
Streptococcus pyogenes PIU 2548	NN
Micrococcus luteus ATCC 9341	OO
Micrococcus luteus ATCC 4698	PP
Escherichia coli JUHL	QQ
Escherichia coli SS	RR
Escherichia coli DC-2	SS
Candida albicans CCH 442	TT
Mycobacterium smegmatis ATCC 114	UU
Nocardia Asteroides ATCC 99700	VV
Haemophilus influenzae DILL AMP R	WW
Streptococcus Pneumonia ATCC 6303	XX
Streptococcus Pneumonia GYR 1171	YY
Streptococcus Pneumonia 5979	ZZ
Streptococcus Pneumonia 5649	ZA

Table 1
Antibacterial Activity (MIC's) of Selected Compounds

	Ery. A standard	Example 2	Example 3	Example 4	Example 5	Example 6	Example 7
AA	0.2	0.2	0.2	0.39	0.2	0.2	0.1
BB	3.1	12.5	12.5	6.2	12.5	12.5	3.1
CC	>100	>100	>100	>100	>100	>100	>100
EE	0.39	0.39	0.39	0.39	0.39	0.39	0.39
GG	>100	>100	>100	>100	>100	>100	>100
HH	0.39	0.2	0.39	0.39	0.2	0.2	0.2
JJ	0.02	0.02	0.05	0.02	0.02	0.02	0.1
KK	0.05	0.05	0.1	0.05	0.05	0.05	0.1
LL	0.05	0.05	0.05	0.05	0.05	0.05	0.05
MM	>100	>100	>100	>100	>100	>100	>100
NN	6.2	6.2	6.2	6.2	6.2	6.2	6.2
PP	0.2	0.39	0.39	0.39	0.39	0.39	0.2
QQ	>100	50	50	50	50	50	100
RR	0.78	0.78	0.39	0.78	0.78	0.78	0.39
TT	>100	>100	>100	>100	>100	>100	>100
UU	3.1	6.2	6.2	6.2	6.2	6.2	6.2
VV	0.1	0.1	0.1	0.05	0.1	0.1	0.05
WW	4	8	8	4	4	4	8
XX	0.06	0.06	0.06	0.03	0.06	0.06	0.12
YY	0.06	0.06	0.06	0.03	0.03	0.03	0.12
ZZ	>128	>128	>128	>128	>128	>128	>128
ZA	16	16	8	8	8	8	16

Synthetic Methods

Abbreviations

Abbreviations which have been used in the descriptions of the schemes and the examples that follow are: Ac for acetate; Bz for benzoyl; dba for dibenzylidene acetone; CDI for carbonyldiimidazole; DCM for dichloromethane; DMA for N,N-dimethylacetamide; DMAP for 4-(N,N-dimethylamino)pyridine; DME for dimethoxyethane; DMF for N,N-dimethylformamide; DMS for dimethylsulfide; DMSO for dimethylsulfoxide; dppb for 1,4-bis(diphenylphosphino)butane; EDCI for 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; HMPA for hexamethylphosphoramide; MTBE for methyl *tert*-butyl ether; TEA for triethylamine; TFA for trifluoroacetic acid; THF for tetrahydrofuran; and TBAB for tetrabutylammonium bromide.

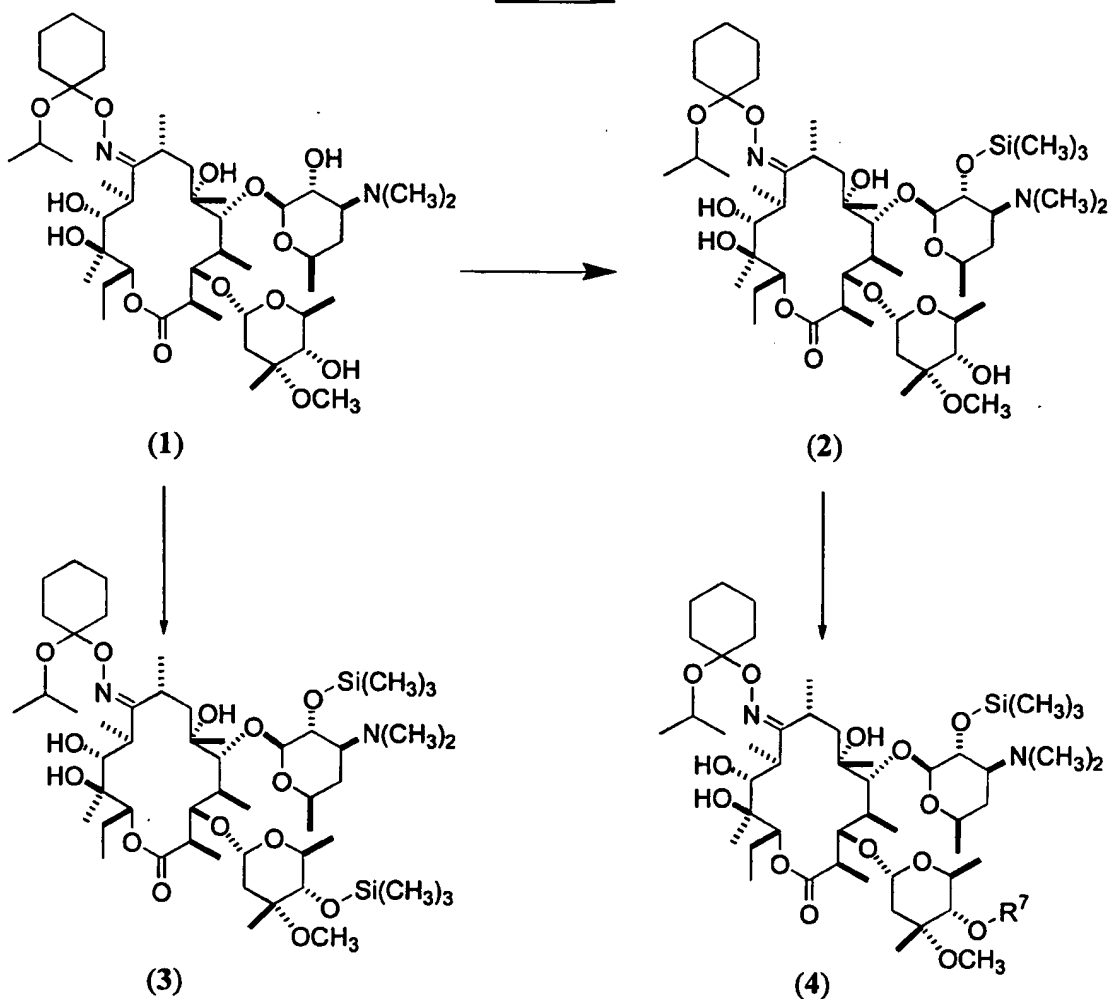
The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes which illustrate the methods by which the compounds of the invention can be prepared. The compounds defined above can be prepared by a variety of synthetic routes. Representative procedures are shown below in Schemes 1-14. The groups R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ are defined above, and the groups X¹, X², X³, and X⁴ are defined below. It will be readily apparent to one of ordinary skill in the art that the compounds defined above can be synthesized by substitution of the appropriate reactants and agents in the syntheses shown below. It will also be apparent to one skilled in the art that the selective protection and deprotection steps, as well as the order of the steps themselves, can be carried out in varying order, depending on the nature of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸, to successfully complete the syntheses of compounds defined above. A thorough discussion of protecting groups is provided in Greene and Wuts, Protective Groups in Organic Synthesis, 2nd ed., John Wiley & Son, Inc., 1991, the relevant portions of which are incorporated herein by reference.

The groups R¹, R¹³, R⁶, R⁷, R⁴ and R⁵ together, and R⁵ and R⁶ together, when each is other than hydrogen, can be introduced to the erythronolide ring (for R¹, R¹³, R⁶, R⁴ and R⁵ together, and R⁵ and R⁶ together) or cladinose ring (for R⁷) from precursor compounds R¹-X¹, R¹³-X¹, R⁶-X¹, X¹-(CH₂)_x-X¹ or X¹-C(O)-X¹, and R⁷-X¹, respectively. In each case, X¹ is an attachment group comprising a halo or sulfonate leaving group or a carbonyl activating group. The precursor compounds are commercially available or can be prepared from commercially available starting materials. For example, compounds containing an alcohol group can be elaborated to alkyl, alkenyl, alkynyl, aldehyde, ether, acid halide, ester, amide, amine, oxime, thioalkoxide, sulfinyl, sulfonyl, or carboxylic acid-containing groups by means well known in the art. Many of these groups can be further elaborated to

other groups such as carbonates, carbamates, or ureas. Functional group transformations useful for preparing precursor compounds R^1-X^1 , $R^{13}-X^1$, R^6-X^1 , $X^1-(CH_2)_x-X^1$ or $X^1-C(O)-X^1$, and R^7-X^1 are disclosed in Larock, "Comprehensive Organic Transformations. A Guide to Functional Group Preparations," VCH Publishers, New York (1989), the relevant portions of which are incorporated herein by reference. The introduction of these groups to the erythronolide or cladinose ring is discussed in the schemes.

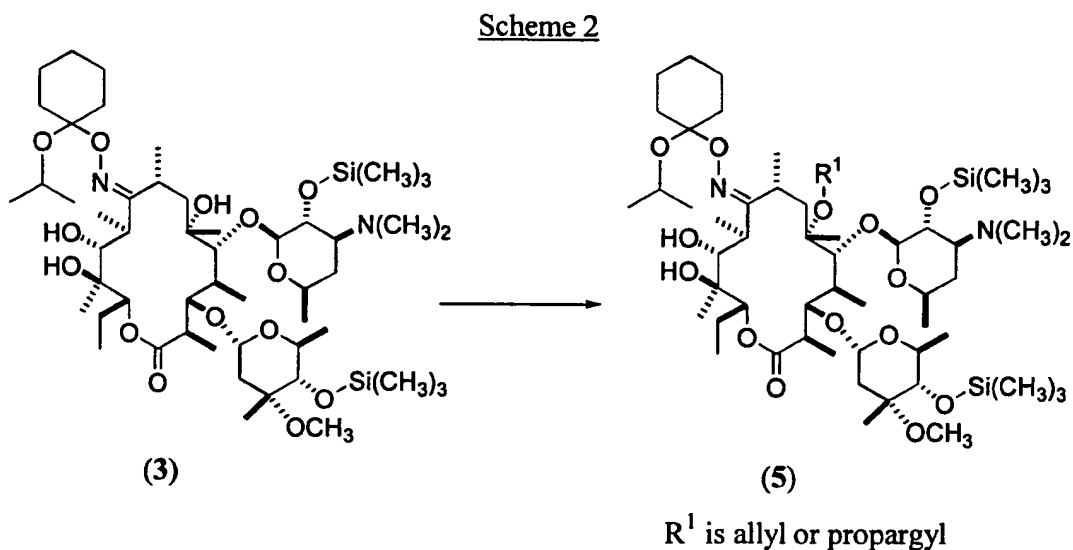
Compounds of formula (1) in Scheme 1 can be prepared from erythromycin A. The synthesis is described in United States Patents 4,990,602, 4,331,803, and 4,670,549, the relevant portions of which are incorporated herein by reference. The C-9-carbonyl of erythromycin A can be protected as an oxime. Preferred protecting groups of the C-9-carbonyl are $=N-O-R^x$ or $=N-O-C(R^y)(R^z)(OR^x)$, wherein R^x is (a) $-C_1-C_{12}$ -alkyl, (b) $-C_1-C_{12}$ -alkyl substituted with aryl, (c) $-C_1-C_{12}$ -alkyl substituted with substituted aryl, (d) $-C_1-C_{12}$ -alkyl substituted with heteroaryl, (e) $-C_1-C_{12}$ -alkyl substituted with substituted heteroaryl, (f) $-C_3-C_{12}$ -cycloalkyl, or (g) $-Si(R^a)_3$, wherein R^a is $-C_1-C_{12}$ -alkyl or aryl, and wherein R^y and R^z are independently (a) hydrogen, (b) $-C_1-C_{12}$ -alkyl, (c) $-C_1-C_{12}$ -alkyl substituted with aryl, or (d) $-C_1-C_{12}$ -alkyl substituted with substituted aryl, or R^y and R^z taken together with the carbon to which they are attached form a $-C_3-C_{12}$ -cycloalkyl ring. A particularly preferred carbonyl protecting group for the C-9-carbonyl of erythromycin A is O-(1-isopropoxycyclohexyl) oxime, wherein R^y and R^z together are cyclohexyl and R^x is isopropyl.

Scheme 1



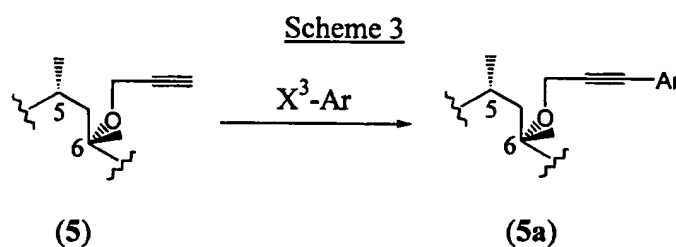
As shown in Scheme 1, the 2'-hydroxy of the desosamine ring and 4''-hydroxy of the cladinose ring of compounds of formula (1) can be protected sequentially or simultaneously by treatment of the same with hydroxy protecting group precursors to provide compounds of formulas (2) or (3), respectively. Hydroxy protecting group precursors include, acetic anhydride, benzoic anhydride, hexamethyldisilazane, a trialkylsilyl or triarylsilyl halide, or benzyl chloroformate under controlled conditions to preclude demethylation of the cladinose dimethylamine group. Preferred protecting groups include acetyl, benzoyl, and trimethylsilyl. A particularly preferred protecting group precursor is trimethylsilyl chloride. Compounds of formula (2) can be further elaborated to compounds of formula (4) by treatment of the former with R⁷-X¹, wherein X¹ is halide, and base. When derivatizing compounds of formula (1), acid can be liberated with the progress of the reaction. For this reason, the reactions described in Scheme 1 are usually run with at least a stoichiometric amount of base present. Examples of such bases include pyridine, diisopropylethylamine, and TEA. Although the solvent used in the

reaction is not particularly limited, a solvent which is not reactive with the starting materials and in which the starting materials are both soluble is generally used. Examples of such solvents include acetone, acetonitrile, diethyl ether, DCM, chloroform, ethyl acetate, THF, dioxane, or mixtures thereof. Other factors determine the product disposition, as well. For example, treatment of compounds of formula (1) with one equivalent of a hydroxy protecting group precursor and base at room temperature usually results in compounds of formula (2). Treatment of compounds of formula (1) with two equivalents of a hydroxy protecting group precursor and base with catalytic DMAP at room temperature or elevated temperature usually results in compounds of formula (3). The reaction time is generally 30 minutes to 18 hours and can be selected depending on the desired product disposition.

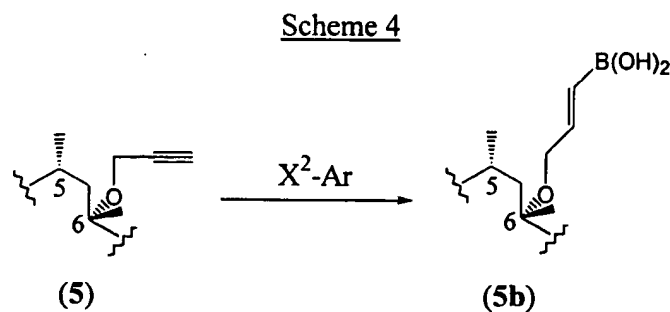


The conversion of compounds of formula (3) to compounds of formula (5) is shown in Scheme 2. Alkylation of compounds of formula (3) can be accomplished by treatment of the former with R^1-X^1 in the presence of base as described in US 5,866,549, the relevant portions of which are incorporated herein by reference, and in the experimentals below. An alternative preparation of compounds of formula (I), wherein R^1 is allyl ($-C_3$ -alkenyl), is treatment of compounds of formula (I) with R^1-X^2 , wherein R^1 is allyl ($-C_3$ -alkenyl) or a substituted alkyl and X^2 is a *tert*-butyl carbonate moiety, in the presence of a catalyst such as $Pd_2(dba)_3$, as described in commonly owned pending US application Serial No. _____, filed June 24, 1999 and in Example 1, Step 1(c). Although the solvent used in these reactions is not particularly limited, a solvent which is not reactive with the starting materials and in which the starting materials are both soluble is generally used. Examples of such solvents include diethyl ether, DME, THF, dioxane, or mixtures thereof. When employing R^1-X^1 to derivatize the 6-position, acid is liberated

with the progress of the reaction, so it is preferable to run the reaction in the presence of a suitable deacidifying agent. For this reason, the reaction is usually run in with at least a stoichiometric amount of base present. Examples of such bases include pyridine, diisopropylethylamine, TEA, potassium hydroxide, cesium hydroxide, tetraalkylammonium hydroxide, sodium hydride, potassium hydride, and alkali metal alkoxides such as potassium isopropoxide, potassium *tert*-butoxide, and potassium isobutoxide. The reactions generally proceed at room temperature but can be run at lower or elevated temperatures, as needed. The reaction time is generally 30 minutes to 18 hours and can be selected depending on the types of method chosen.



Intraconversion compounds of the invention is also shown in Scheme 3. Compounds of formula (5), wherein R¹ is propargyl, can be further elaborated to compounds of formula (5a) by a number of general routes. A preferred general route is shown in Scheme 3. The 6-O propargyl group can be reacted with groups such as X³-Ar wherein Ar is an unsubstituted or a substituted aryl group or heteroaryl group, respectively, and X³ is one of any number of covalent bond precursors such as halides (preferably bromide and iodide) and sulfonates. The coupling reactions are performed in the presence of Pd(II) or Pd(0) catalysts with promoters such as phosphines (preferably triphenylphosphine), arsines (preferably triphenylarsine), amines (preferably pyridine and triethylamine), and inorganic bases (preferably potassium carbonate or cesium fluoride) in polar, aprotic solvents such as benzene, toluene, DMF, DMSO, DME, acetonitrile THF, or mixtures thereof at temperatures from about room temperature to about 150 °C, depending on the coupling method chosen and the nature of X³.



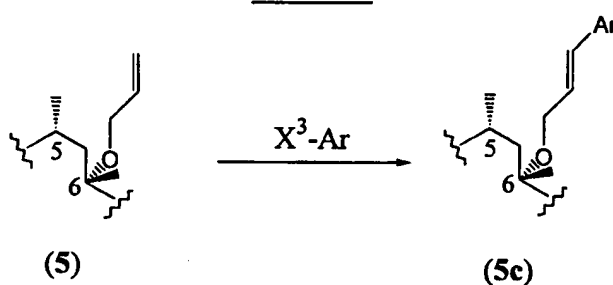
Intraconversion compounds of the invention is also shown in Scheme 4.

Compounds of formula (5), wherein R¹ is propargyl, can be still further elaborated intermediates of formula (5b) with borane-THF in aprotic solvents at temperatures from about -20 °C to about room temperature to provide vinyl boronic acid derivatives.

Intermediates (5b) then be reacted under Suzuki conditions with X³-Ar reagents, catalysts, and promoters described in Scheme 3 to provide additional compounds of formula (5). A thorough discussion of Suzuki conditions is provided in Chemical Reviews, 1995, Vol. 95, No.7, 2457-2483, the relevant portions of which are incorporated herein by reference.

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Scheme 5



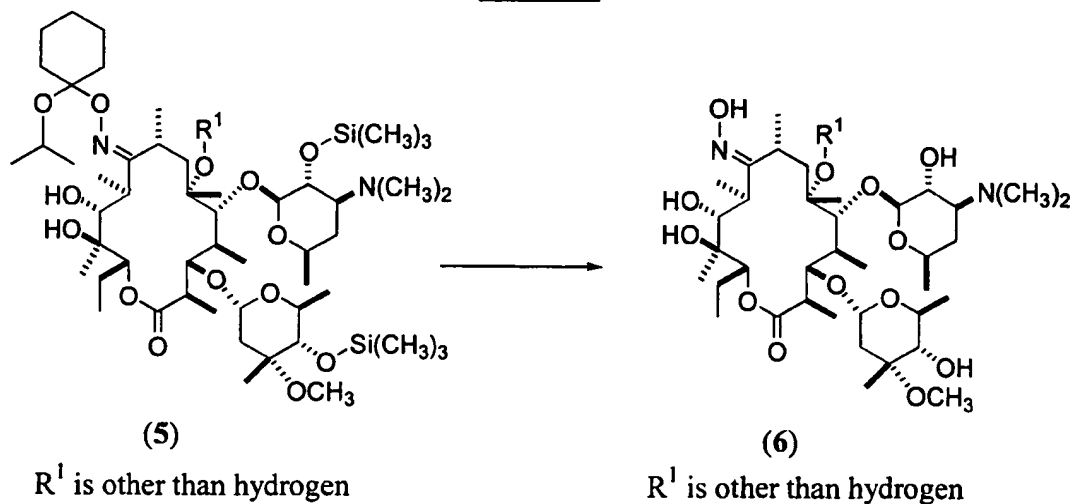
Intraconversion compounds of the invention is also shown in Scheme 5.

Compounds of formula (5) can be still even further elaborated to compounds of formula (5c) by treatment with to X³-Ar reagents under Heck conditions, the conditions of which

are described in Larock (op. cit.) and in US 5,866,549 (Example 1 steps 1a-g and Example 102, steps 120a-c), incorporated herein by reference.

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Scheme 6

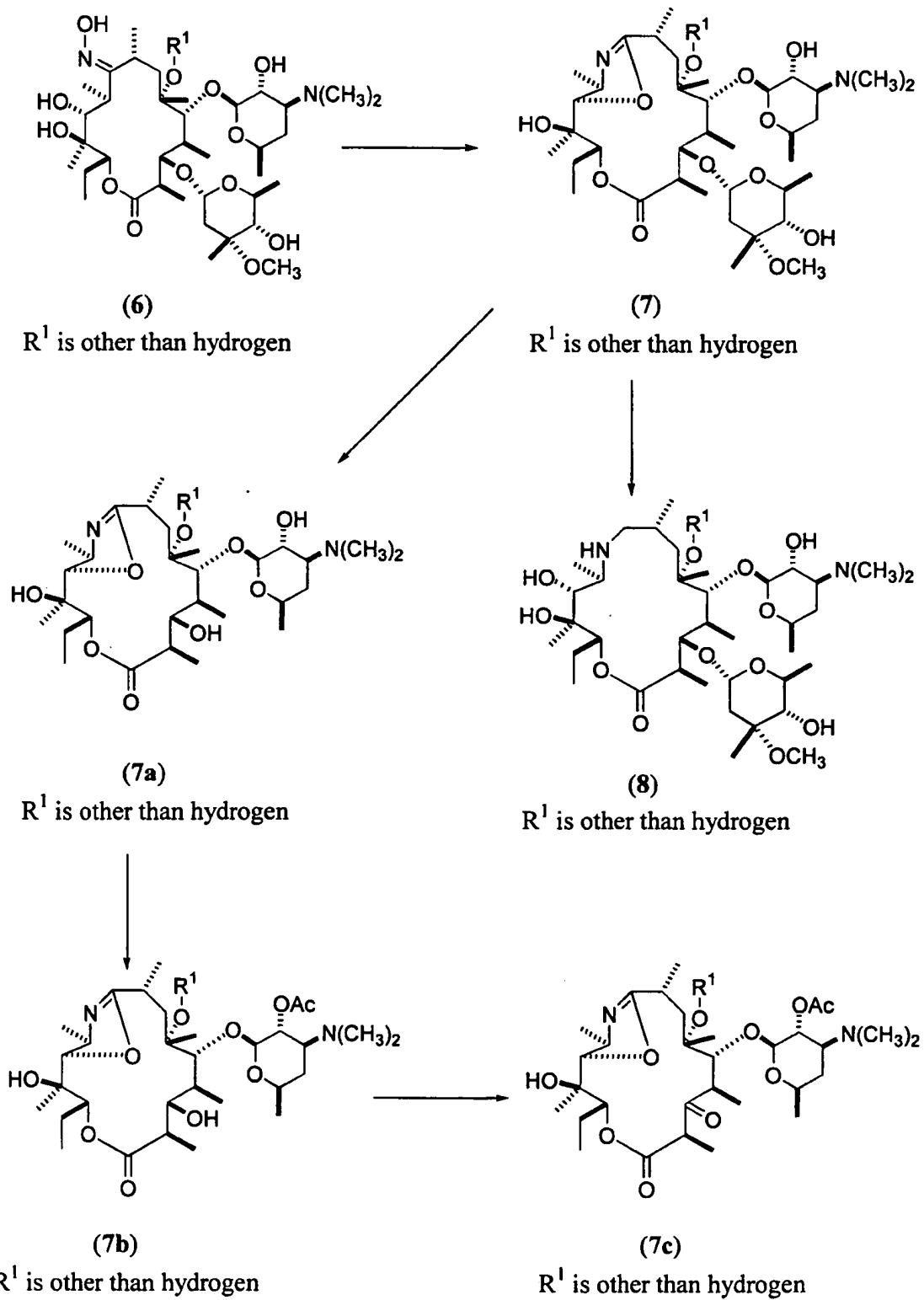


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As shown in Scheme 6, the conversion of compounds of formula (5) to compounds of formula (6) can be accomplished by treatment of the former with an acid such as HCl, HBr, acetic acid, or TFA. Although the solvent used in these reactions is not particularly

limited, a solvent which is not reactive with the starting material and in which the starting material and the acid are both soluble is generally used. Examples of such solvents include acetonitrile, DME, THF, dioxane, or mixtures thereof. The preferred conditions for the deprotection of the 2'- and 4"-hydroxy groups of the desosamine and cladinose rings, respectively, (acetic acid in acetonitrile and water) usually result in concomitant removal of the 1-isopropoxycyclohexyl group provide the unalkylated oxime (=N-OH) at C-9.

Scheme 7



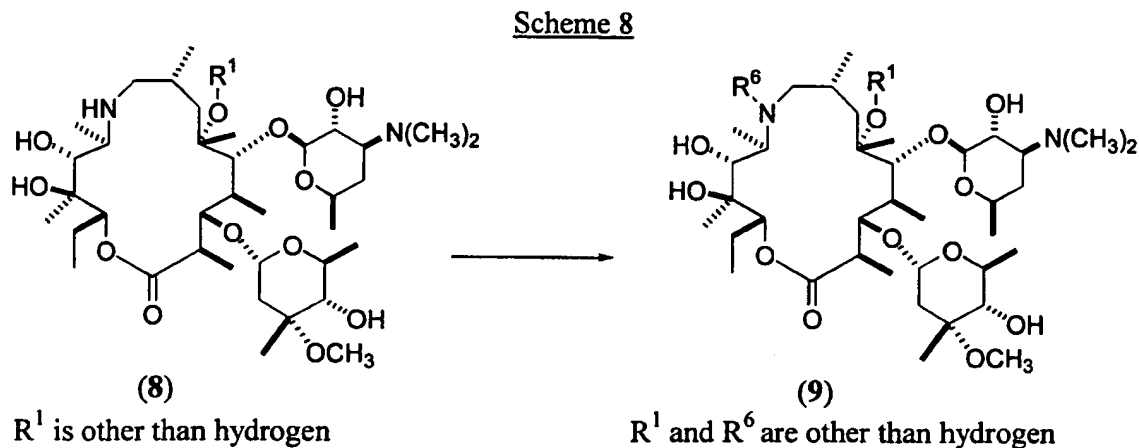
Synthesis of compounds of formula (III), intraconversion of compounds of formula (III) to compounds of formula (IV) and the conversion of compounds of formula (III) to compounds of formula (I) is shown in Scheme 7. Compounds of formula (6) can be

5 treated with oxime activating agents to provide compounds of formula (7). Especially preferred oxime activating agents are sulfonyl halides such as para-toluenesulfonyl chloride, methanesulfonyl chloride, para-bromosulfonyl chloride, and para-bromosulfonyl chloride. When using sulfonyl halides to activate oximes, acid is liberated with the progress of the reaction, so it is preferable to run the reaction in the presence of a suitable deacidifying agent. For this reason, the reaction is run with at least a stoichiometric amount of base present. Examples of such bases include pyridine, diisopropylethylamine, TEA, NaHCO₃, Na₂CO₃, KHCO₃, and K₂CO₃. Conversion of compounds of formula (7) to compounds of formula (8) can be achieved by treatment of the former with reducing agents such as PtO₂, borane in tetrahydrofuran, borane dimethylsulfide, sodium cyanoborohydride, or sodium borohydride optionally in the presence of an acid such as TiCl₄, CoCl₂, AlCl₃, methanesulfonic acid, or acetic acid. In a particularly preferred embodiment, compounds of formula (6) are treated with para-toluenesulfonyl chloride and pyridine in THF to provide compounds of formula (7) which are treated with NaBH₃CN and acetic acid to provide compounds of formula (8). Although the solvent used in these reactions is not particularly limited, a solvent which is not reactive with the starting materials and in which the starting materials are both soluble is generally used. Examples of such solvents include acetone, water, acetonitrile, diethyl ether, DME, DCM, chloroform, DMF, DMA, ethyl acetate, THF, dioxane, N-methylpyrrolidinone, DMSO, diethylsulfoxide, HMPA, or mixtures thereof. The reactions generally proceed at room temperature but can be run at lower temperatures. The reaction time is generally 30 minutes to 18 hours and can be selected depending on the types of starting materials and reaction temperature.

25 Alternatively, compounds of formula (7) can be converted to compounds of formula (7a) by hydrolysis with dilute aqueous acid or by enzymatic hydrolysis of the former to remove the cladinose moiety from the 3-hydroxy cladinose group. Representative acids include hydrochloric acid, sulfuric acid, perchloric acid, chloroacetic acid, dichloroacetic acid, or TFA. Although the solvent used in the reaction is not particularly limited, a solvent which is not reactive with the starting materials and in which the starting materials are both soluble is generally used. Examples of such solvents include acetone, acetonitrile, C₁-C₄-alcohols, THF, dioxane, or mixtures thereof. The preferred reaction temperature is about -10 °C to about 60 °C and depends on the method chosen. Reaction times are typically about 0.5 to about 24 hours.

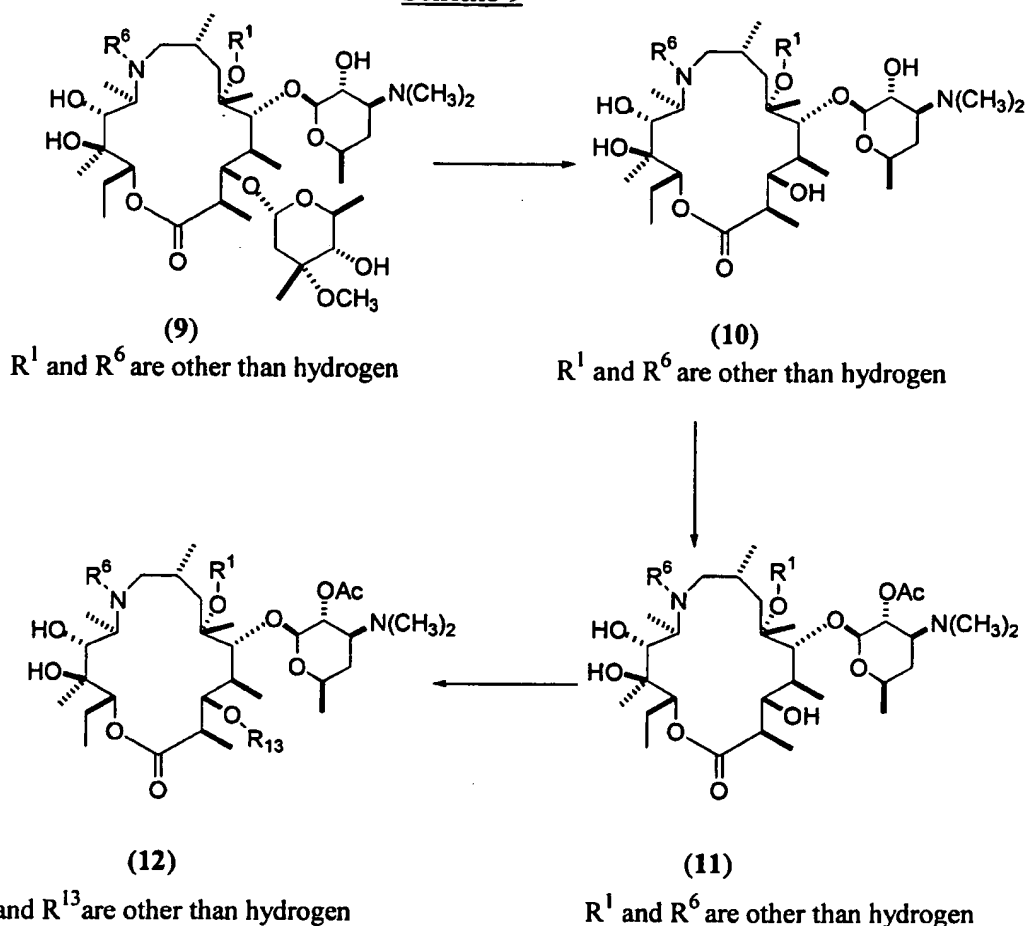
35 Compounds of formula (7a) can be converted to compounds of formula (7c) by treatment of the former with a 2'-hydroxyl protecting group to provide compounds of formula (7b) followed by oxidation of the 3-hydroxy group to a 3-oxo group using a Corey-Kim reaction with N-chlorosuccinimide-dimethyl sulfide, a Moffat oxidation with a

carbodiimide-DMSO complex in the presence of pyridinium trifluoroacetate, or Dess-Martin periodinane. In a preferred embodiment, compounds of formula (7b) are added to a preformed N-chlorosuccinimide-dimethyl sulfide complex in a chlorinated solvent such as DCM or chloroform at about -10 °C to about 25 °C. After stirring for about 0.5 to about 4 hours, a tertiary amine such as TEA or diisopropylethylamine is added to produce compounds of formula (7c).



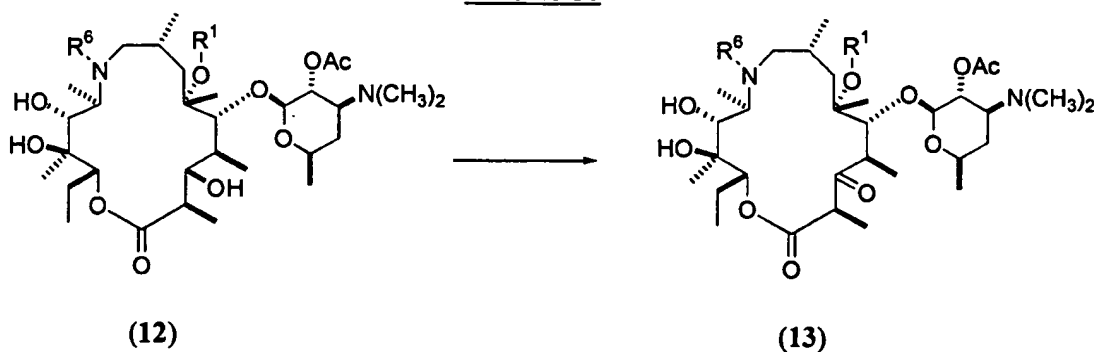
Intraconversion of compounds of formula (I) are shown in Scheme 8. Compounds of formula (8) can be converted to compounds of formula (9) by treatment of the former with alkylating agent R^6-X^1 , wherein X^1 is a halo leaving group, in the presence of base. An alternative means of converting compounds of formula (8) to compounds of formula (9) is treatment of the former with alkylating agent R^6-X^4 , wherein X^4 is a carboxaldehyde group, in the presence of formic acid. Although the solvent used in the reaction is not particularly limited, a solvent which is not reactive with the starting materials and in which the starting materials are both soluble is generally used. Examples of such solvents include acetone, acetonitrile, diethyl ether, DCM, chloroform, ethyl acetate, THF, dioxane, or mixtures thereof. The reaction generally proceeds at elevated temperatures but can be run at lower temperatures. The reaction time is generally 30 minutes to 18 hours and can be selected depending on the types of starting materials and reaction temperature. In a particularly preferred embodiment, R^6-X^3 is reacted with (8) in chloroform at elevated temperatures.

Scheme 9



Conversion of compounds of formula (I) to compounds of formula (II) and intraconversion compounds of formula (II) are shown in Scheme 9. Compounds of formula (9) can be converted to compounds of formula (10) by hydrolysis with dilute aqueous acid or by enzymatic hydrolysis to remove the cladinose moiety from the 3-hydroxy cladinose group. Representative acids include hydrochloric acid, sulfuric acid, perchloric acid, chloroacetic acid, dichloroacetic acid, or TFA. Although the solvent used in the reaction is not particularly limited, a solvent which is not reactive with the starting materials and in which the starting materials are both soluble is generally used. Examples of such solvents include acetone, acetonitrile, C_1 - C_4 -alcohols, THF, dioxane, or mixtures thereof. The preferred reaction temperature is about -10 °C to about 60 °C and depends on the method chosen. Reaction times are typically about 0.5 to about 24 hours. Compounds of formula (10) can then be converted to compounds of formula (11) by the hydroxyl protection described for compounds of formula (1) in Scheme 1. Conversion of compounds of formula (11) to compounds of formula (12) can be achieved by treatment of the former with R^{13} - X^1 , wherein X^1 is a carbonyl-activating group.

Scheme 10

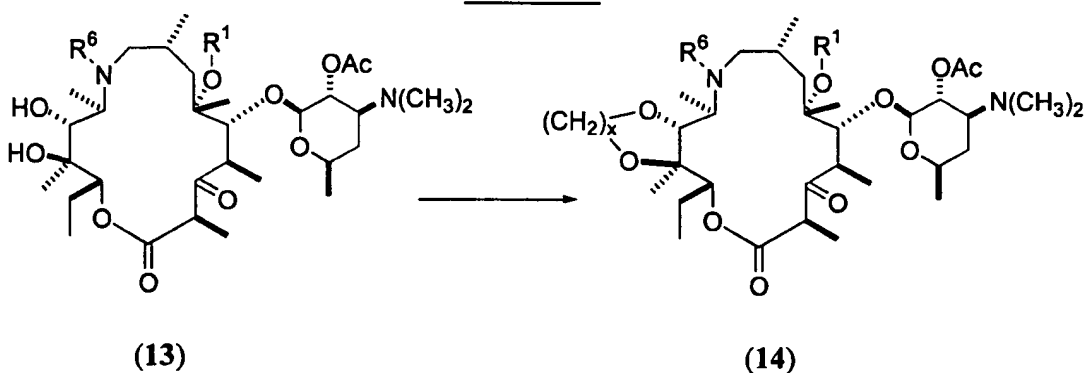


R^1 and R^6 are other than hydrogen

R^1 and R^6 are other than hydrogen

Intraconversion compounds of formula (II) is shown in Scheme 10. Conversion of compounds of formula (12) to compounds of formula (13) can be accomplished by oxidation of the 3-hydroxy group to a 3-oxo group using a Corey-Kim reaction with N-chlorosuccinimide-dimethyl sulfide, a Moffat oxidation with a carbodiimide-DMSO complex in the presence of pyridinium trifluoroacetate, or Dess-Martin periodinane. In a preferred embodiment, compounds of formula (12) are added to a preformed N-chlorosuccinimide-dimethyl sulfide complex in a chlorinated solvent such as DCM or chloroform at about $-10\text{ }^{\circ}\text{C}$ to about $25\text{ }^{\circ}\text{C}$. After stirring for about 0.5 to about 4 hours, a tertiary amine such as TEA or diisopropylethylamine is added to produce compounds of formula (13).

Scheme 11

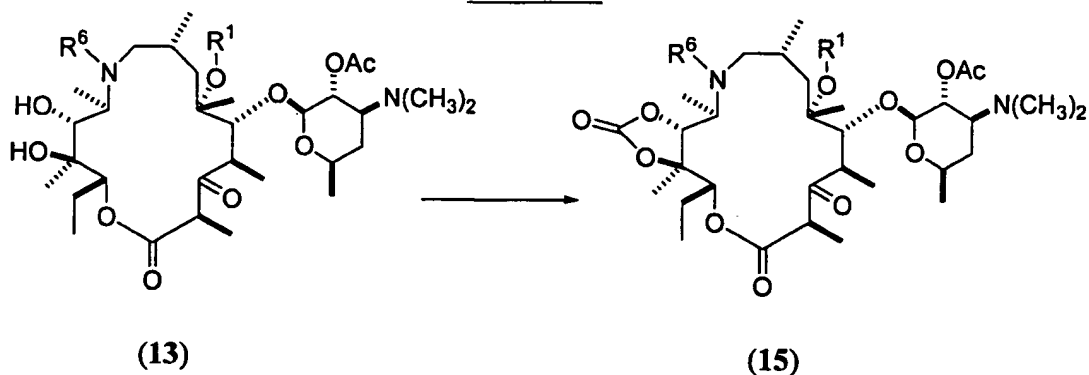


R^1 and R^6 are other than hydrogen

R^1 and R^6 are other than hydrogen

Intraconversion compounds of formula (II) is also shown in Scheme 11. Conversion of compounds of formula (13) to compounds of formula (14) can be achieved by treatment of the former with a bifunctional alkylating agent such as $X^1-(CH_2)_x-X^1$, wherein X^1 is a halo leaving group, in the presence of base, using the same conditions as described for the introduction of R^1 to compounds of formula (3) in Scheme 2.

Scheme 12

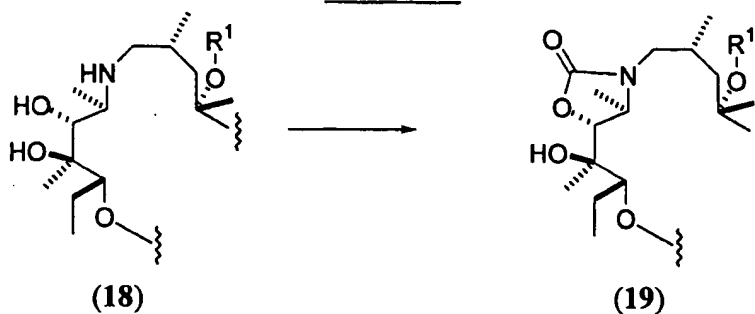


R¹ and R⁶ are other than hydrogen

R¹ and R⁶ are other than hydrogen

Intraconversion compounds of formula (II) is also shown in Scheme 12.

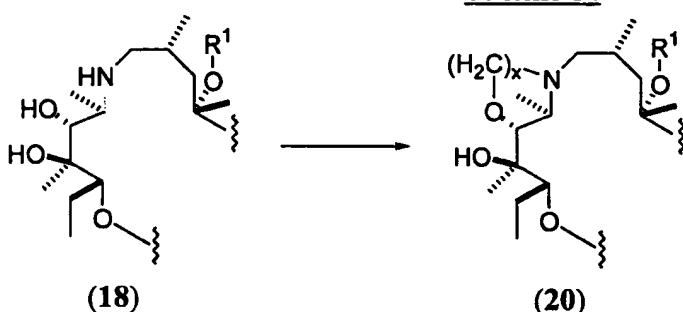
Conversion of compounds of formula (13) to compounds of formula (15) can be achieved
5 by treatment of the former with a carbonyl-activating group such as CDI, phosgene or
triphosgene in the presence of base. When using phosgene or trophosgene to derivatize
compounds of formula (13), acid is liberated with the progress of the reaction, so it is
preferable to run the reaction in the presence of a suitable deacidifying agent. For this
reason, the reaction is run with at least a stoichiometric amount of base present. Examples
10 of such bases include pyridine, diisopropylethylamine, TEA, NaHCO₃, Na₂CO₃, KHCO₃,
and K₂CO₃. Although the solvent used in these reactions is not particularly limited, a
solvent which is not reactive with the starting materials and in which the starting materials
are both soluble is generally used. Examples of such solvents include acetone,
acetonitrile, DME, DCM, chloroform, DMF, DMA, ethyl acetate, THF, dioxane, benzene,
15 toluene, or mixtures thereof. The reactions generally proceed at lower temperatures but
can be run at higher temperature. The reaction time is generally 30 minutes to 18 hours
and can be selected depending on the types of starting materials and reaction temperature.

Scheme 13R¹ is other than hydrogenR¹ is other than hydrogen

Intraconversion compounds of the invention is also shown in Scheme 13.

Compounds of formula (18) can be treated with carbonyl activating groups as described for compounds of formula (13) in Scheme 12 to provide compounds of formula (19).

5

Scheme 14R¹ is other than hydrogenR¹ is other than hydrogen

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Intraconversion compounds of the invention is also shown in Scheme 13.

Compounds of formula (18) can be treated with a X¹-(CH₂)_x-X¹ as described for compounds of formula (13) in Scheme 11 to provide compounds of formula (20).

The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

15

Clarithromycin (3-O-cladinosyl-5-O-desosaminyl-6-O-methyl-erythronolide A) was obtained from Abbott Laboratories. All other starting materials not mentioned specifically by example were purchased from Aldrich Chemical Company (Milwaukee, WI).

20

Example 1

Compound of formula (III): R¹ is -CH₂CH=CH₂, R⁴ is hydrogen, R⁷ is hydrogen, R⁸ is hydrogen

5 Step 1a: Compound (1) from Scheme 1

The desired product was prepared as described in US 4,990,602, Examples (1) and (2), and substituting 1-cyclohexen-1-yl isopropyl ether for 2-methoxypropene.

Step 1b: allyl *tert*-butyl carbonate

10 The desired product was prepared as described in the Canadian Journal of Chemistry, 1985, Vol.63, pp.153-162.

Step 1c: Compound (5) from Scheme 2: R¹ is -CH₂CH=CH₂, R⁴ is hydrogen, R⁵ is hydrogen, R⁷ is -Si(CH₃)₃, R⁸ is -Si(CH₃)₃, R^x is iso-propyl, R^y and R^z together are cyclohexyl

15 A mixture of Pd₂(dba)₃ (0.120 g, 0.131mmol) and dppb (111 mg, 0.259 mmol) was treated with the product from Step 1a (azeotropically dried with toluene, 25.0 g, 24.23 mmol) and the product from Step 1b (4.6 g, 29.1 mmol) in THF (100 mL), heated to reflux for 30 minutes, cooled, and concentrated. The concentrate was dissolved in ethyl acetate (250 mL), and the resulting solution was washed with half-saturated Na₂CO₃ and brine,
20 dried (Na₂SO₄), filtered, and concentrated to provide 25.2 g of the desired product of sufficient purity for use without further purification.
MS (DCI/NH₃) *m/z* 1073 (M+H)⁺.

Step 1d: Compound (6) from Scheme 6: R¹ is -CH₂CH=CH₂, R⁴ is hydrogen, R⁵ is hydrogen, R⁷ is hydrogen, R⁸ is hydrogen, R^x is hydrogen

25 A suspension of the product from Step 1c (25.2 g, 23.5 mmol) in acetonitrile (240 mL) and water (50 mL) was treated with glacial acetic acid (70 mL), and the resulting solution was stirred at room temperature for 3 days and concentrated. The concentrate was dissolved in DCM (100 mL), and the resulting solution was washed sequentially with half-saturated Na₂CO₃ (until the pH of the wash was 10), water, and brine, dried (Na₂SO₄),
30 filtered, and concentrated to provide 17.4 g of the desired product of sufficient purity for use without further purification.
MS (DCI/NH₃) *m/z* 790 (M+H)⁺.

Step 1e: Compound of formula (III): R¹ is -CH₂CH=CH₂, R⁴ is hydrogen, R⁷ is hydrogen, R⁸ is hydrogen

A solution of the product from Step 1d (7.0 g, 8.88 mmol) in pyridine (90 mL) at 0 °C was treated over 30 minutes with a solution of para-toluenesulfonyl chloride (3.39 g, 17.77 mmol) in THF (90 mL), stirred for 2.5 hours, heated to 40 °C for 20 hours, cooled, and treated with ethyl acetate (200 mL). The resulting solution was washed sequentially with half-saturated Na₂CO₃, water, and brine, dried (Na₂SO₄), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 96:4 acetone/TEA to provide 2.86 g of the desired product.
MS (DCI/NH₃) *m/z* 771 (M+H)⁺.

Example 2

Compound of formula (I): R¹ is -CH₂CH=CH₂, R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is hydrogen, R⁷ is hydrogen, R⁸ is hydrogen

A solution of Example 1 (100 mg, 0.13 mmol) and one crystal of bromocresol green in methanol (1 mL) at room temperature was treated with glacial acetic acid until the color of the solution changed from blue to yellow, treated a first time with NaBH₃CN (16 mg, 0.26 mmol), stirred at room temperature for 18 hours, treated a second time with NaBH₃CN (16 mg, 0.260 mmol), stirred for 4 hours, treated a third time with NaBH₃CN (32 mg, 0.52 mmol), stirred for 3 hours, and treated a fourth time with NaBH₃CN (32 mg, 0.52 mmol), and stirred for 16 hours, treated with 1M NaOH (5 mL), and extracted with MTBE. The extract was washed with brine, dried (Na₂SO₄), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 9:1:0.5 DCM/methanol/concentrated NH₄OH to provide 15.1 mg of the desired product.
MS (DCI/NH₃) *m/z* 775 (M+H)⁺.

Example 3

Compound of formula (I): R¹ is -CH₂CH=CH₂, R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is methyl, R⁷ is hydrogen, R⁸ is hydrogen

A solution of Example 2 (840 mg, 1.09 mmol) in chloroform (20 mL) at room temperature was treated dropwise with a mixture of formic acid (90 μL, 2.39 mmol) and 37% aqueous formaldehyde (196 μL, 7.05 mmol), heated to reflux for 15 hours, cooled, and treated with half-saturated Na₂CO₃ (50 mL). The layers were separated and the aqueous layer was extracted with chloroform. The extract was washed with water and brine, dried (Na₂SO₄), filtered and concentrated to provide 1.0 g of the desired product of sufficient purity for use without further purification.
MS (DCI/NH₃) *m/z* 789 (M+H)⁺.

Example 4

Compound of formula (II): R¹ is -CH₂CH=CH₂, R² is hydrogen, R³ is -OR¹³, R¹³ is hydrogen, R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is methyl, R⁸ is hydrogen

5 A solution of Example 3 (757 mg, 0.972 mmol) in 90% ethanol (15 mL) was treated with water (30 mL), treated with 1M HCl (4.86 mL, 4.86 mmol), stirred at room temperature for 15.5 hours, and concentrated. The concentrate was dissolved in water (50 mL), and the resulting solution was washed with MTBE, made basic (pH 10) with half-saturated Na₂CO₃, and extracted with isopropyl acetate. The extract was washed with
10 brine (50 mL), dried (Na₂SO₄), filtered, and concentrated to provide 637 mg of the desired product of sufficient purity for use without further purification.
MS (DCI/NH₃) *m/z* 631 (M+H)⁺.

Example 5

15 Compound of formula (II): R¹ is -CH₂CH=CH-(3-quinolinyl), R² and R³ together are oxo, R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is methyl, R⁸ is hydrogen

Step 5a: Compound (12) in Scheme 10: R¹ is -CH₂CH=CH₂, R² is hydrogen, R³ is -OR¹³, R¹³ is hydrogen, R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is methyl, R⁸ is -C(O)CH₃

20 A solution of Example 4 (590 mg, 0.937 mmol) in DCM (12 mL) at room temperature was treated sequentially with TEA (196 μL, 1.41mmol) and acetic anhydride (133 μL, 1.41 mmol), stirred for 20 hours, diluted with DCM (25 mL), washed with saturated NaHCO₃ and brine (25 mL), dried (Na₂SO₄), filtered, and concentrated to provide 654 mg of the desired product of sufficient purity for use without further
25 purification.
MS (DCI/NH₃) *m/z* 673 (M+H)⁺.

Step 5b: (Option 1): Compound (13) in Scheme 11: R¹ is -CH₂CH=CH₂, R² is hydrogen, R³ and R⁴ together are oxo, R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is methyl, R⁸ is -C(O)CH₃

30 A solution of the product from Step 5a (25 mg, 0.037 mmol) in DCM (1 mL) at room temperature was treated sequentially with DMSO (73 μL, 1.02 mmol) and EDCI (57 mg, 0.29 mmol), stirred for 30 minutes, treated with pyridinium trifluoroacetate (58 mg, 0.29 mmol), stirred at room temperature for 44 hours, treated with water (10 mL), and extracted with DCM. The extract was washed with saturated NaHCO₃ and brine, dried
35 (Na₂SO₄), filtered, and concentrated to provide 21.8 mg of the desired product of sufficient purity for use without further purification.
MS (DCI/NH₃) *m/z* 671 (M+H)⁺.

Step 5b (Option 2): Compound (13) in Scheme 11: R¹ is -CH₂CH=CH₂, R² is hydrogen, R³ and R⁴ together are oxo, R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is methyl, R⁸ is -C(O)CH₃

A solution of the product from Step 5a (200 mg, 0.298 mmol) in DCM (3 mL) at 0 °C was treated with Dess-Martin periodinane (139 mg, 0.33 mmol), stirred for 30 minutes, warmed to room temperature, stirred for 2.5 hours, treated with half-saturated Na₂CO₃ (25 mL), and extracted with DCM. The extract was washed with half-saturated Na₂CO₃ and brine, dried (Na₂SO₄), filtered, and concentrated. The concentrate was purified by flash chromatography on silica gel with 99:1:1 DCM/methanol/concentrated NH₄OH to provide 51 mg of the desired product.

MS (DCI/NH₃) *m/z* 671 (M+H)⁺.

Step 5c: Compound (13) in Scheme 11: R¹ is -CH₂CH=CH-(3-quinolinyl), R² is hydrogen, R³ and R⁴ together are oxo, R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is methyl, R⁸ is -C(O)CH₃

A mixture of the product from Step 5b, (133 mg, 0.167 mmol) 3-bromoquinoline (42 μL, 312 mmol), TBAB (76 mg, 0.327 mmol), diisopropylethylamine (103 μL, 0.592 mmol), and palladium (II) acetate (33 mg, 0.147 mmol) in DME (5 mL) in a sealed tube was heated at 80 °C for 16 hours, cooled to room temperature, treated with half-saturated Na₂CO₃ (15 mL), and extracted with ethyl acetate. The extract was washed sequentially with half-saturated Na₂CO₃, water, and brine, dried (Na₂SO₄), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 99:1:1 DCM/methanol/concentrated NH₄OH to provide 58.6 mg of the desired product.

MS (DCI/NH₃) *m/z* 798 (M+H)⁺.

Step 5d: Compound of formula (II): R¹ is -CH₂CH=CH-(3-quinolinyl), R² and R³ together are oxo, R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is methyl, R⁸ is hydrogen

A solution of the product from Step 5c (70 mg, 0.088 mmol) in methanol (5 mL) was stirred at room temperature for 40 hours and concentrated. The concentrate was purified by flash column chromatography on silica gel with 98:2:1 DCM/methanol/concentrated NH₄OH to provide 15 mg of the desired product.

MS (DCI/NH₃) *m/z* 756 (M+H)⁺.

Example 6

Compound of formula (II): R¹ is -CH₂CH=CH-(3-quinolinyl), R² and R³ together are oxo,

R⁴ and R⁵ together are -C(O)-, R⁶ is methyl, R⁸ is hydrogen

Step 6a: Compound (15) from Scheme 12: R¹ is -CH₂CH=CH-(3-quinolinyl), R² and R³ together are oxo, R⁴ and R⁵ together are -C(O)-, R⁶ is methyl, R⁸ is -C(O)CH₃

A solution of the product from Step 5c (59 mg, 0.074 mmol) in DCM (1.5 mL) was treated with pyridine (28 μ L, 0.221 mmol), cooled to -10 °C, treated with triphosgene (218 mg, 0.074 mmol), stirred for 2 hours, treated with additional pyridine (3 drops) and triphosgene (10 mg), stirred for 21 hours, treated with ethyl acetate (15 mL) and DCM (15 mL), and washed half-saturated Na₂CO₃. The wash was extracted with DCM, and the combined extracts were washed with brine, dried (Na₂SO₄), and concentrated. The concentrate was purified by flash chromatography on silica gel with 99:1:1 DCM/methanol/concentrated NH₄OH to provide 34.2 mg of the desired product. MS (DCI/NH₃) *m/z* 824 (M+H)⁺.

Step 6b: Compound of formula (II): R¹ is -CH₂CH=CH-(3-quinolinyl), R² and R³ together are oxo, R⁴ and R⁵ together are -C(O)-, R⁶ is methyl, R⁸ is hydrogen

A solution of Example 12 (34 mg, 0.042 mmol) in methanol (2.5 mL) was stirred at room temperature for 20 hours and concentrated to provide 28.5 mg of the desired product of sufficient purity for use without further purification. MS (DCI/NH₃) *m/z* 782 (M+H)⁺.

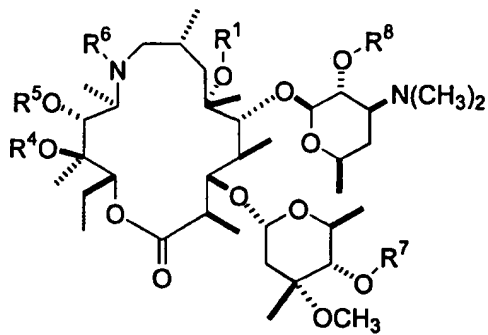
Example 7

Compound of formula (I): R¹ is -CH₂CH=CH-(3-quinolinyl), R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is methyl, R⁷ is hydrogen, R⁸ is hydrogen

A mixture of Example 3, 3-bromoquinoline (26 μ L, 0.19 mmol), tri(o-tolyl)phosphine (6 mg, 0.019 mmol), TEA (53 μ L, 39 mg, 0.381 mmol), and palladium (II) acetate (3 mg, 0.013 mmol) in acetonitrile (2.5 mL) in a sealed tube was heated at 60 °C for 1 hour and at 90 °C for 20 hours, cooled to room temperature, and treated with ethyl acetate (25 mL) and half-saturated Na₂CO₃ (25 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate. The extract was washed with water and brine, dried (Na₂SO₄), filtered, and concentrated. The concentrate was purified by flash column chromatography on silica gel with 9:1:0.5 DCM/methanol/concentrated NH₄OH to provide 25 mg of the desired product. MS (DCI/NH₃) *m/z* 916 (M+H)⁺.

WHAT IS CLAIMED IS:

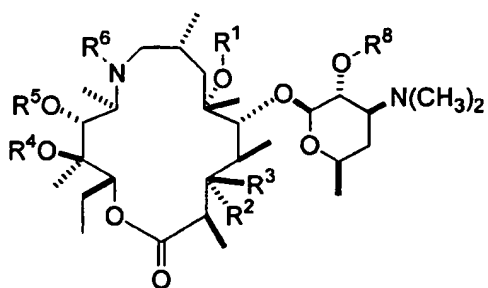
1. A compound selected from the group consisting of compounds of formula (I)



(I),

5

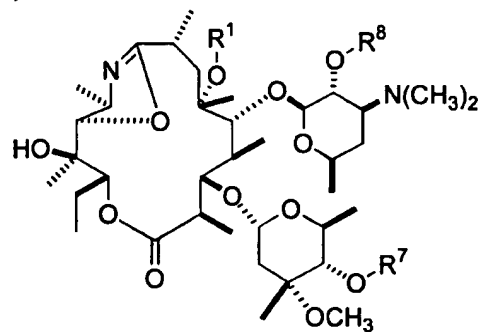
compounds of formula (II)



(II),

10

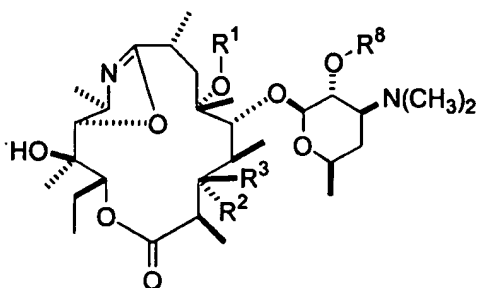
compounds of formula (III)



(III),

and

compounds of formula (IV)



(IV),

or pharmaceutically acceptable salts or prodrugs thereof, wherein, in formulas (I)-(IV), R¹ and R⁶ are independently selected from the group consisting of

- 5 (1) hydrogen,
 (2) -C₁-C₁₂-alkyl,
 (3) -C₃-C₁₂-alkenyl,
 and
 (4) -C₃-C₁₂-alkynyl,

10 wherein (2)-(4) can be optionally substituted with one, two, or three substituents independently selected from the group consisting of

- (a) halogen,
 (b) -OR⁹, wherein R⁹ is selected from the group consisting of

- 15 (i) hydrogen,
 (ii) -C₁-C₁₂-alkyl,
 (iii) -C₂-C₁₂-heteroalkyl,

wherein (ii) and (iii) can be optionally substituted with one, two, or three substituents independently selected from the group consisting of

- 20 (1') aryl,
 (2') substituted aryl,
 (3') heteroaryl,
 and
 (4') substituted heteroaryl,

- 25 (iv) aryl,
 (v) substituted aryl,
 (vi) heteroaryl,
 and
 (xv) substituted heteroaryl,

(c) -NR¹¹R¹², wherein R¹¹ and R¹² are independently selected from the group consisting of

- 30 (i) hydrogen,

(ii) -C₁-C₁₂-alkyl,

(iii) -C₂-C₁₂-heteroalkyl,

wherein (ii) and (iii) can be optionally substituted with one, two, or three substituents independently selected from the group consisting of

(1') aryl,

(2') substituted aryl,

(3') heteroaryl,

and

(4') substituted heteroaryl,

(iv) aryl,

(v) substituted aryl,

(vi) heteroaryl,

and

(xv) substituted heteroaryl,

or

R¹¹ and R¹², together with the atom to which they are attached, form a

heterocycloalkyl ring, wherein the heterocycloalkyl ring can be optionally substituted,

(d) =N-O-R⁹, wherein R⁹ is defined above,

(e) aryl,

(f) substituted aryl,

(g) heteroaryl,

(h) substituted heteroaryl,

(i) -C₃-C₈-cycloalkyl,

(j) substituted -C₃-C₈-cycloalkyl,

(k) heterocycloalkyl,

(l) substituted heterocycloalkyl,

(m) -NHC(O)R⁹, wherein R⁹ is defined above,

(n) -NHC(O)OR¹⁰, wherein R¹⁰ is selected from the group consisting of

(i) -C₁-C₁₂-alkyl,

(ii) -C₁-C₁₂-heteroalkyl,

wherein (i) and (ii) can be optionally substituted with one, two, or three substituents independently selected from the group consisting of

(1') aryl,

(2') substituted aryl,

(3') heteroaryl,

and

(4') substituted heteroaryl,

(iii) aryl,

(iv) substituted aryl,

(v) heteroaryl,

5 and

(vi) substituted heteroaryl,

(o) -NHC(O)NR¹¹R¹², wherein R¹¹ and R¹² are defined above,

(p) -OC(O)R¹⁰, wherein R¹⁰ is defined above,

(q) -OC(O)OR¹⁰, wherein R¹⁰ is defined above,

10 (r) -OC(O)NR¹¹R¹², wherein R¹¹ and R¹² are defined above,

(s) -C(O)R⁹, wherein R⁹ is defined above,

(t) -CO₂R⁹, wherein R⁹ is defined above,

and

(u) -C(O)NR¹¹R¹², wherein R¹¹ and R¹² are defined above;

15

R² is hydrogen;

R³ is -OR¹³, wherein R¹³ is selected from the group consisting of

(1) hydrogen,

20 (2) -C(O)R¹⁰, wherein R¹⁰ is defined above,

(3) -CO₂R¹⁰, wherein R¹⁰ is defined above,

and

(4) -C(O)NR¹¹R¹², wherein R¹¹ and R¹² are defined above;

25 or

R² and R³ together are oxo;

R⁴ and R⁵ are hydrogen;

30 or

R⁴ and R⁵ together are -C(O)- or -(CH₂)_x-, wherein x is one, two, or three;

or

R⁵ and R⁶ together are -C(O)- or -(CH₂)_x-, wherein x is defined above;

35

R⁷ is selected from the group consisting of

(1) hydrogen,

- (2) -C₁-C₁₂-alkyl,
(3) -C₃-C₁₂-alkenyl,
(4) -C₃-C₁₂-alkynyl,
(5) -C₂-C₁₂-heteroalkyl,
5 (6) -C₄-C₁₂-heteroalkenyl,
(7) -C₄-C₁₂-heteroalkynyl,

wherein (2)-(7) can be optionally substituted with one, two, or three substituents independently selected from the group consisting of

- (a) halo,
10 (b) hydroxy,
(c) -NR¹¹R¹², wherein R¹¹ and R¹² are defined above,
(d) aryl,
(e) substituted aryl,
(f) heteroaryl,

15 and

- (g) substituted heteroaryl,

(8) -C(O)R⁹, wherein R⁹ is defined above,

(9) -CO₂R⁹, wherein R⁹ is defined above,

and

20 (11) -C(O)NR¹¹R¹², wherein R¹¹ and R¹² are defined above;

and

R⁸ is hydrogen or a hydroxy protecting group;

25 with the proviso that when R² and R³ together are oxo, R¹ is other than hydrogen or unsubstituted methyl.

2. A compound according to Claim 1, wherein R² is hydrogen, R³ is -OR¹³, and R¹³ is hydrogen.

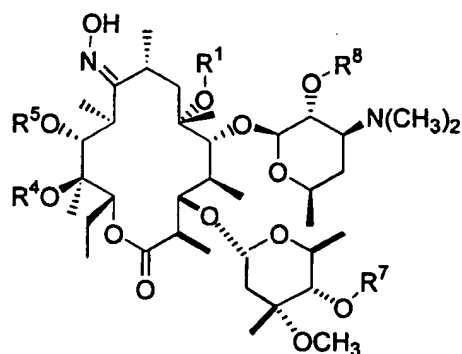
30 3. A compound according to Claim 1, wherein R² and R³ together are oxo.

4. A compound according to Claim 1, wherein R⁴ and R⁵ are hydrogen.

35 5. A compound according to Claim 1, wherein R⁴ and R⁵ together are -C(O)-.

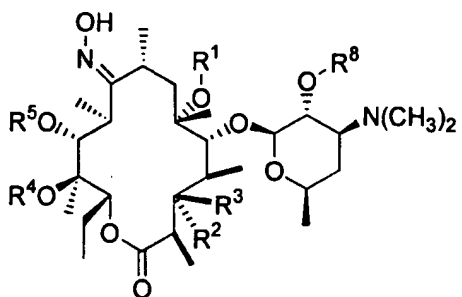
6. A compound according to Claim 1, wherein R⁶ is hydrogen.

7. A compound according to Claim 1, wherein R⁶ is methyl.
8. A compound according to Claim 1, wherein R¹ is -CH₂-CH=CH₂ or
 5 -CH₂-CH=CH-(3-quinolinyl).
9. A compound according to Claim 8, wherein R¹ is -CH₂-CH=CH₂.
10. A compound according to Claim 8, wherein R¹ is -CH₂-CH=CH-(3-quinolinyl).
11. A method for preparing compounds according to Claim 1,
 the method comprising
 (a) reacting compounds of formula (Ia)



(Ia)

or compounds of formula (Ib)



(Ib),

wherein R¹, R², R³, R⁴, R⁵, R⁷, and R⁸ are as defined in Claim 1,
 with an oxime activating agent;

(b) reacting the product from step (a) with a reducing agent;

(c) optionally alkylating the product from step (b);

and

(d) optionally deprotecting the product from step (c).

12. The method according to Claim 11, wherein the oxime activating agent is a sulfonyl halide.

5

13. The method according to Claim 12, wherein the sulfonyl halide is para-toluenesulfonyl chloride, methanesulfonyl chloride, para-bromosulfonyl chloride, or para-bromosulfonyl chloride.

10

14. The method according to Claim 11, wherein the reducing agent is borane in tetrahydrofuran, borane-dimethyl sulfide, sodium cyanoborohydride, or sodium borohydride, optionally in the presence of an acid.

15

15. The method according to Claim 14, wherein the reducing agent is sodium cyanoborohydride in the presence of acid.

16. The method according to Claim 15, wherein the acid is acetic acid.

20

17. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable carrier.

25

19. A compound selected from the group consisting of
Compound of formula (III): R¹ is -CH₂CH=CH₂, R⁴ is hydrogen, R⁷ is hydrogen, R⁸ is hydrogen,

30

Compound of formula (I): R¹ is -CH₂CH=CH₂, R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is hydrogen, R⁷ is hydrogen, R⁸ is hydrogen,

Compound of formula (I): R¹ is -CH₂CH=CH₂, R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is methyl, R⁷ is hydrogen, R⁸ is hydrogen,

35

Compound of formula (II): R¹ is -CH₂CH=CH-(3-quinolinyl), R² and R³ together are oxo, R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is methyl, R⁸ is hydrogen,

Compound of formula (II): R¹ is -CH₂CH=CH-(3-quinolinyl), R² and R³ together are oxo, R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is methyl, R⁸ is hydrogen,

Compound of formula (II): R¹ is -CH₂CH=CH-(3-quinolinyl), R² and R³ together are oxo, R⁴ and R⁵ together are -C(O)-, R⁶ is methyl, R⁸ is -C(O)CH₃,
and

5 Compound of formula (I): R¹ is -CH₂CH=CH-(3-quinolinyl), R⁴ is hydrogen, R⁵ is hydrogen, R⁶ is methyl, R⁷ is hydrogen, R⁸ is hydrogen.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/20363

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07H17/08 A61K31/70 A61P31/04		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07H A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 109 253 A (PFIZER) 23 May 1984 (1984-05-23) examples 2,3 ---	1,4,6, 11-18
X	EP 0 259 789 A (PLIVA PHARM & CHEM WORKS) 16 March 1988 (1988-03-16) claim 1 and examples 7-11 ---	1,4,6, 11-18
X	WILKENING R R ET AL: "Novel Transannular Rearrangements of Azalide Iminoethers" TETRAHEDRON,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 53, no. 50, 15 December 1997 (1997-12-15), pages 16923-16944, XP004106498 ISSN: 0040-4020 page 16927, compounds 17,19 --- -/--	1,4,6, 11-18
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
° Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search 26 October 2000		Date of mailing of the international search report 12. 01 01
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer SCOTT, J

INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/20363

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,4,5,8-19(all partially); 6(completely)

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,4,5,8-19 partially; 6 completely

Compounds of formula I, claim 1, where R6 = H ; their method of preparation and their use

2. Claims: 1,4,5,8-19 partially; 7 completely

Compounds of formula I, claim 1, where R6 = alkyl (optionally substituted) ; their method of preparation and their use

3. Claims: 1,4,5,8-18 partially

Compounds of formula I, claim 1, where R6 = alkenyl (optionally substituted) ; their method of preparation and their use

4. Claims: 1,4,5,8-18 partially

Compounds of formula I, claim 1, where R6 = alkynyl (optionally substituted) ; their method of preparation and their use

5. Claims: 1-5,8-19 partially

Compounds of formula II, claim 1 ; their method of preparation and their use

6. Claims: 1,8-10,17-19 partially

Compounds of formula III, claim 1 ; their method of preparation and their use

7. Claims: 1-3,8-10,17,18 partially

Compounds of formula IV, claim 1 ; their method of preparation and their use

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

P./US 00/20363

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